

REMARKS

Claims 1-38 are pending. Due to a restriction requirement, claims 3-38 are withdrawn from consideration. In the Office action mailed May 30, 2006, claims 1 and 2 have been examined. Claims 1 and 2 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement and further as failing to comply with the written description requirement. Claims 1 and 2 are also rejected under 35 U.S.C. § 102(b) in view of U.S. Patent 5,474,796 (hereafter “Brennan”) and under 35 U.S.C. § 102(e) in view of U.S. Patent 6,582,908 (hereafter “Fodor”). The specification is also objected to. Each of these rejections and the objection are addressed below.

Objection to the specification

The specification is objected because it contains embedded hyperlinks and/or other forms of browser executable code. To address this objection, such text has been deleted from the specification on pages 24, 26, and 44. This amendment adds no new matter. On the basis of this amendment, the objection may be withdrawn.

Amendments to the claims

Claim 1 has been amended to recite “wherein at least two of said nuclear encoded mitochondrial energy metabolism nucleic acid molecules, or fragments thereof, are at least 15 nucleotides in length” and to recite “hybridizable array elements.” Support for

these changes is found, for example, at page 18, line 23, of the specification and at page 45, line 26, of the specification, respectively. New claim 39 has been added. Support for this claim is found, for example, at page 18, line 24, of the specification. These amendments add no new matter.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

The Office has rejected claims 1 and 2 under 35 U.S.C. § 112, first paragraph, on the basis that these claims fail to comply with the enablement requirement. To fulfill the enablement requirement, a claim must be supported by a disclosure that contains sufficient information regarding the claimed subject matter to enable one skilled in the pertinent art to make and use the claimed invention (M.P.E.P. § 2164). Further, experimentation required to practice the claimed invention must not be undue.

As outlined below, claims 1 and 2 are enabled by the instant specification and knowledge in the art. Claim 1 recites a microarray that includes at least two nuclear encoded mitochondrial energy nucleic acids, or fragments thereof, and claim 2 recites specific nuclear encoded mitochondrial energy metabolism genes identified by name and GenBank accession number. The Office asserts that these claims are not enabled on two grounds. The first of these is that a nucleotide sequence is not adequately identified by its GenBank accession number. Second, the Office asserts that it is unpredictable as to which parts of a sequence should be on the array, as the specification provides no details

as to which portions of these sequences have mitochondrial energy metabolism activity. Each of these grounds for rejection is addressed below.

A GenBank accession number specifically and uniquely identifies a sequence

The Office asserts that GenBank accession numbers do not define a sequence because the sequences provided by GenBank numbers can be altered. In making this rejection, the Office cites a specific accession number and asserts (page 5 of the action):

Accession No. AF047436 was submitted on 2/10/1998, but the sequence had an update to its sequence on 11/21/2002. It is unpredictable based on just the Genbank [sic] accession number which sequence was used to create the array. It is undefined if the sequence used was the original sequence submitted or the most recently updated. It is unclear which parts of the sequence has [sic] been changed and the effect of the changes.

Contrary to the Office's assertion, one can in fact determine whether a sequence identified by a GenBank accession number has been changed following its original submission. Revisions to each GenBank sequence are tracked by a version number. This is explained by Benson et al. ("GenBank," *Nucleic Acids Res.* 34(Suppl 1):D16-D20, 2006; page D18, second column), a copy of which is enclosed:

[w]hen a change is made to a sequence given in a GenBank record, a new gi number is issued to the sequence and the version extension of the 'Accession.version' identifier is incremented."

The National Center for Biotechnology Information (NCBI) (Bethesda, Md.) website (<http://www.ncbi.nlm.nih.gov/Sitemap/samplerecord.html>; Exhibit A) further notes:

If there is any change to the sequence data (even a single base), the version number will be increased, e.g., U12345.1 → U12345.2, but the accession portion will remain stable.”

In the case of GenBank accession number AF047436, version 1 of the sequence appears on GenBank (Exhibit B). By using the “Sequence Revision History” (see <http://www.ncbi.nlm.nih.gov/entrez/sutils/girevhist.cgi>) available in the GenBank database, one can confirm whether the sequence associated with a particular accession number has been changed. The history of accession number AF047436, for example, indicates the entry associated with this accession number has been modified three times following its initial submission. None of the revisions, however, include a change to the nucleotide sequence, as evidenced by each revision reciting the same version number (Exhibit C). Indeed, Applicants’ representative has confirmed the four versions of AF047436 in the Sequence Revision History contain the same sequence.

In contrast to the Office’s assertion that one would be unable to determine what sequence is referred to by a GenBank accession number, Applicants have shown that a GenBank number provides reference to a specific sequence and that the GenBank database tracks the changes to each sequence associated with an accession number. As the sequence referred to in the specification can be readily determined by one of skill in the art, the present specification is enabling in this regard.

The invention is enabled even in view of possible changes to GenBank sequences

The Office further asserts that changes to sequences in the GenBank database could render one of skill in the art unable to practice the claimed invention. Applicants disagree. Sequences useful for arrays have been provided in the present specification. Applicants submit that, even if the sequences identified in the application are modified in the GenBank database after filing, such changes would not render one of skill in the art unable to make or use the claimed microarrays. The nucleotides used to form microarrays of the invention function only as hybridizable array elements. Where hybridizable array elements constitute only a portion of the complete sequence, changes may occur outside these elements. Also, such elements can function even in the presence of sequence changes, as an exact sequence match with a nucleic acid applied to the array is not required for hybridization to take place. The sequences provided in Applicants' specification fully enable the production of claimed arrays, and the Office's concern in this regard is unwarranted.

The Office has not demonstrated that potential sequence changes are a practical issue

Moreover, even if sequences in the GenBank database are theoretically subject to change, the Office has failed to demonstrate that the potential for such changes represents a practical issue preventing one of skill in the art from making or using the claimed invention. Of the five sequences selected for initial examination (Accession numbers

X83218, AF087135, U09813, D16562, and AF047436), none has undergone a sequence revision following filing of the present application, as indicated by the Sequence Revision History in the GenBank database. Nor has the Office provided any evidence that the mere potential for such changes would prevent one of skill in the art from practicing the invention as claimed. On this basis as well, Applicants submit that the enablement rejection should be withdrawn.

Recitation of the sequence of a known gene is not required for enablement

Applicants also point out that identification of a gene with a known sequence by name is sufficient to identify the sequence associated with that gene. The Federal Circuit has stated that it is unnecessary to recite known gene sequences in a patent application to satisfy either the enablement or written description requirements (*Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 79 U.S.P.Q.2d 1001 (Fed. Cir. 2006)). In *Falkner*, the court held that identification of a known group of genes by group name (“essential genes”) was sufficient to support a claim reciting that group. Determining a known sequence from the name of a gene or a known group of genes would not require undue experimentation, as the sequences of such genes are readily available in sequence databases such as GenBank, as well as in the literature available at the time of filing. By providing both gene names and GenBank accession numbers, Applicants have more than met their burden under the enablement requirement with regard to nuclear encoded mitochondrial energy metabolism

genes generally and with regard to the specific genes recited in the claims. On this basis as well, the enablement rejection should be withdrawn.

Nucleic acids of the array need not provide mitochondrial energy metabolism activity

The Office also rejects claims 1 and 2 on the basis that it is unpredictable as to which parts of a sequence should be on the array, as the specification does not indicate which portions of the sequence retain mitochondrial energy metabolism activity. The Office's concern in this regard is misplaced. The nucleic acids in the claimed arrays need not encode functional proteins. Rather, they need only provide sequences to which other nucleic acids hybridize. As indicated in Applicants' specification, for example, at pages 46-47, the nucleic acids hybridized to the claimed array are typically mRNAs that include the entire coding sequence of mitochondrial energy metabolism genes. Because these mRNAs themselves include the full coding sequences, the nucleic acids of the array need not encode any particular fragment (except that it must include a hybridizable element), and certainly need not encode fragments with mitochondrial energy metabolism function. Nor, for the same reason, is it necessary to determine whether nucleic acids used in the arrays of the invention possess such activity.

To determine whether a nucleic acid can be used in an array of the invention, one would simply determine whether the sequence can hybridize to an appropriate test nucleic acid, for example, an mRNA encoding a mitochondrial energy metabolism protein. Both

the art and the instant specification (see, e.g., page 47) provide extensive guidance on this step. Experimentation required to make these determinations is routine in the art. Such experimentation does not present an undue burden, and the enablement rejection on this basis should also be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

Claims 1 and 2 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. A patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (M.P.E.P. § 2164).

As outlined below, each element of the claimed invention is sufficiently described in the specification. The Office, however, rejects the claims on three grounds. First, the claims are rejected on the basis that mitochondrial energy metabolism nucleic acids are not adequately described. The Office asserts (page 8 of the action):

The claims encompass nucleic acids defined by Genebank [*sic*] accession numbers which can be update [*sic*] and would therefore comprise any nucleic acid variant of any size, fragments of the sequence presented. The claims would encompass updates to the Genebank accession number could have variants, which include nucleotide substitutions, additions, deletions, translocations, and truncations. The specification does not describe the sequences encompassed by “nuclear encoded mitochondrial energy metabolism nucleic acid.”

Applicants have provided evidence (above) that changes to sequences in the GenBank database are tracked by the sequence version number and the Sequence Revision History

in the GenBank database, and that reference to a sequence by its GenBank accession number specifically describes a unique sequence. Applicants have also noted that the current specification provides a written description of sequences that can be used for microarray production and changes to GenBank sequences, even if they theoretically occurred, would generally not interfere with the use of these sequences in the arrays of the invention. Applicants submit that the identification of exemplary nuclear encoded mitochondrial energy genes by both name and GenBank accession number sufficiently describes the hybridizable array elements of the invention. The written description rejection on this basis should therefore be withdrawn.

Second, the Office asserts that the nucleic acids used in the arrays of the invention are not adequately described as follows (page 8 of the action):

The claims also encompass a large genus of sequence of any size with no defining characteristics to nuclear encoded mitochondrial energy metabolism nucleic acid[s]. An array of sequences could all be 5 mer in length and be considered as having at least 90% of the nucleic acids as nuclear encoded mitochondrial energy metabolism nucleic acid...

Without assenting to this rejection, Applicants have amended claim 1 to recite “wherein at least two of said nuclear encoded mitochondrial energy metabolism nucleic acid molecules, or fragments thereof, are at least 15 nucleotides in length.” In view of this amendment, Applicants submit that this basis for the written description rejection has been rendered moot and should be withdrawn.

Third, the Office asserts the claims fail to meet the written description requirement on the basis that (pages 9-10 of the action) “the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids in view of the species disclosed.” Applicants disagree. The written description requirement can be met by providing either structure or functional characteristics when coupled with a known or disclosed correlation between function and structure (M.P.E.P. § 2163.01(II)(A)(3)(a) and *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002)). Applicants have met this requirement by providing both structure, i.e., exemplary nuclear encoded mitochondrial energy metabolism nucleic acids, and function, i.e., ability to hybridize when used in an array, in the present application. Regarding structure, there is a substantial body of literature describing nuclear encoded mitochondrial energy metabolism genes; it is therefore not necessary for the present specification to include sequences of such genes which are well known and described in the art. In this regard, the Federal Circuit has recently held (*Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 79 U.S.P.Q.2d 1001 (Fed. Cir. 2006)):

Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here “essential genes”), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences.

Regarding function, the nucleic acids used in an array of the invention must have the ability to hybridize to an appropriate nucleic acid, such as an mRNA encoding a mitochondrial energy metabolism gene. Without assenting to the Office's rejection, claim 1 has been amended to recite that at least two of the nuclear encoded mitochondrial energy metabolism nucleic acids are "hybridizable array elements," thereby reflecting this function. For these reasons, the written description rejection should be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) in view of Brennan and under 35 U.S.C. § 102(e) in view of Fodor. The Office asserts that Brennan teaches an array which contains every possible permutation of a 10-mer, and states that this array would inherently include 10-mer fragments of the elected molecules. The Office asserts that Fodor teaches a 2-mer array which includes all possible oligonucleotides containing two base positions and likewise states that this would also inherently include 2-mer fragments of the elected molecules.

To anticipate a claim, a reference must teach each and every limitation of that claim. Applicants submit that Brennan does not teach an array where at least 90% of the nucleic acid molecules on the support are mitochondrial energy metabolism nucleic acid molecules. While Applicants acknowledge that every permutation of a 10-mer nucleic acid would theoretically include sequences of mitochondrial energy metabolism nucleic

acids, this collection of random permutations would not result in an array in which 90% of the nucleic acid molecules on the array would correspond to sequences of mitochondrial energy metabolism nucleic acids. Further, claim 1 has been amended to recite “wherein at least two of said nuclear encoded mitochondrial energy metabolism nucleic acid molecules are at least 15 nucleotides in length.” Brennan does not teach such an array, being limited to a collection of 10-mers. Brennan therefore does not teach each and every limitation of amended claim 1 or its dependent claim 2. The rejection under 35 U.S.C. § 102(b) in view of Brennan should be withdrawn.

With regard to the 2-mer array taught by Fodor, Applicants direct the Office to amended claim 1. Fodor does not teach an array including at least two nuclear encoded mitochondrial energy metabolism nucleic acids, or fragments thereof, bound to a solid support where 90% of the nucleic acids on the support are mitochondrial energy metabolism genes and where at least two of the nuclear encoded mitochondrial energy metabolism nucleic acids are at least 15 nucleotides in length. Thus, this reference cannot anticipate amended claim 1 or its dependent claim 2. The rejection under 35 U.S.C. § 102(e) in view of Fodor should likewise be withdrawn.


CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the Office action for three (3) months, to and including November 30, 2006, and a check in payment of the required extension fee. Also enclosed is a check in the amount of \$25.00 in payment of one additional dependent claim as required by 37 C.F.R. § 1.16(i).

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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